NEW DRUG APPROVAL

Brand Name	Tpoxx®
Generic Name	tecovirimat
Drug Manufacturer	Siga Technologies

New Drug Approval

FDA approval date: May 18, 2022

Review designation: Standard; Orphan

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 214518

Dispensing restriction: Strategic National Stockpile

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Smallpox is a serious, contagious, and sometimes deadly disease caused by the variola virus. Smallpox outbreaks occurred for thousands of years, but the disease was eliminated from the world after a successful vaccination campaign. People with smallpox had a fever and a distinctive skin rash. Although most people with smallpox recovered, about three out of every ten people with the disease died.

Thousands of years ago, variola virus (smallpox virus) emerged and began causing illness and deaths in human populations, with smallpox outbreaks occurring from time to time.

The origin of smallpox is unknown. The finding of smallpox-like rashes on Egyptian mummies suggests that smallpox has existed for at least 3,000 years. The earliest written description of a disease like smallpox appeared in China in the 4th century CE (Common Era). Early written descriptions also appeared in India in the 7th century and in Asia Minor in the 10th century.

The last natural outbreak of smallpox in the United States happened in 1949. The last naturally spread case in the entire world happened in 1977. The World Health Assembly declared smallpox eradicated in 1980. Even a single confirmed case of smallpox today would be considered an emergency.

Efficacy

The effectiveness of Tpoxx® for treatment of smallpox disease has not been determined in humans because adequate and well-controlled field trials have not been feasible and inducing smallpox disease in humans to study the drug's efficacy is not ethical. Therefore, the effectiveness of Tpoxx® for treatment of smallpox disease was established based on results of adequate and well-controlled animal efficacy studies of non-human primates and rabbits infected with non-variola orthopoxviruses. Survival rates observed in the animal studies may not be predictive of survival rates in clinical practice.

Study Design Efficacy studies were conducted in cynomolgus macaques infected with monkeypox virus, and New Zealand white (NZW) rabbits infected with rabbitpox virus. The primary efficacy endpoint for these studies was survival. In non-human primate studies, cynomolgus macaques were lethally challenged intravenously with 5 x 107 plaque-forming units of monkeypox virus; tecovirimat was administered orally once daily at a dose level of 10 mg/kg for 14 days, starting at Day 4, 5 or 6 post-challenges. In rabbit studies, NZW rabbits were lethally challenged intradermally with 1,000 plaque-forming units of rabbitpox virus; tecovirimat was administered orally once daily for 14 days at a dose level of 40 mg/kg, starting at Day 4 post-challenge. The timing of tecovirimat dosing in these studies was intended to assess efficacy when treatment is initiated after animals have developed clinical signs of

disease, specifically dermal pox lesions in cynomolgus macaques, and fever in rabbits. Clinical signs of disease were evident in some animals at Day 2-3 post-challenge but were evident in all animals by Day 4 post-challenge. Survival was monitored for 3-6 times the mean time to death for untreated animals in each model. Study Results Treatment with tecovirimat for 14 days resulted in statistically significant improvement in survival relative to placebo, except when given to cynomolgus macaques starting at Day 6 post-challenge (Table 1).

Table 1: Survival Rates in Tecovirimat Treatment Studies in Cynomolgus Macaques and NZW Rabbits Exhibiting Clinical Signs of Orthopoxvirus Disease

	Treatment Initiation[a]	Survival Percentage (No. survived/n)		p-value[b]	Survival Rate Difference[c] (95% CI)[d]
		Placebo	Tecovirimat		
Cynomolgus Macaques					
Study 1	Day 4	0% (0/7)	80% (4/5)	0.0038	80% (20.8%, 99.5%)
Study 2	Day 4	0% (0/6)	100% (6/6)	0.0002	100% (47.1%, 100%)
Study 3	Day 4	0% (0/3)	83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 5		83% (5/6)	0.0151	83% (7.5%, 99.6%)
	Day 6		50% (3/6)	0.1231	50% (-28.3%, 90.2%)
NZW Rabbits					
Study 4	Day 4	0% (0/10)	90% (9/10)	< 0.0001	90% (50.3%, 99.8%)
Study 5	Day 4	NA[e]	88% (7/8)	NA	NA

[a] Day post-challenge tecovirimat treatment was initiated.

[b] p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma = 0.000001) compared to placebo.

[c] Survival percentage in tecovirimat treated animals minus survival percentage in placebo treated animals.

[d] Exact 95% confidence interval based on the score statistic of difference in survival rates.

[e] A placebo control group was not included in this study.

NA = Not Applicable

Tpoxx® Injection (incidence ≥ 4%): administration site reactions and headache.

Safety

ADVERSE EVENTS

The safety of multiple doses of 240 mg of Tpoxx® injection for intravenous infusion was evaluated in 26 healthy adult subjects ages 23-62 years, inclusive.

The most frequently reported adverse reactions included infusion site pain, infusion site swelling, infusion site erythema, infusion site extravasation, and headache. Adverse reactions that occurred in at least 4% of subjects in the Tpoxx® treatment group are shown in Table 2.

Three subjects (12%) had their treatment with Tpoxx® injection discontinued due to adverse reactions. One subject had two adverse reactions. Each of these subject's adverse reactions (with severity) are listed below:

- Moderate Infusion site extravasation
- Mild Infusion site extravasation
- Mild Infusion site swelling and mild infusion site pain.

Table 2: Treatment-Related Adverse Reactions Reported in ≥ 4% of Healthy Adult Subjects Receiving at Least One Dose of Tpoxx® Injection 240 mg		
	Tpoxx® 240 mg N =26 (%)	Placebo N = 6 (%)
Infusion Site Pain	73	67
Infusion Site Swelling	39	67
Infusion Site Erythema	23	67
Infusion Site Extravasation	19	50
Headache	15	0

Clinically significant adverse reactions that were reported in < 4% of subjects exposed to Tpoxx® injection and at rates higher than subjects who received placebo are listed below:

- General and administration site: infusion site discomfort, infusion site edema.
- Musculoskeletal and connective tissue: myalgia, arthritis, back pain, muscle tightness.
- Gastrointestinal: diarrhea.
- Eye: photophobia.
- Skin and Subcutaneous Tissue: pruritus generalized.

WARNINGS & PRECAUTIONS

Hypoglycemia When Co-Administered with Repaglinide Co-administration of repaglinide and tecovirimat may cause mild to moderate hypoglycemia. Monitor blood glucose and monitor for hypoglycemic symptoms when administering Tpoxx® with repaglinide. In a drug interaction study, 10 of 30 healthy subjects experienced mild (6 subjects) or moderate (4 subjects) hypoglycemia following co-administration of repaglinide (2 mg) and Tpoxx® capsules. Symptoms resolved in all subjects after intake of food and/or oral glucose.

Risks of Hydroxypropyl-β-Cyclodextrin Excipient for Patients with Renal Insufficiency and Pediatric Patients < 2 Years of age

Patients with renal insufficiency Tpoxx® Injection: In healthy patients and in patients with mild to severe renal insufficiency, the majority of an 8 g dose of hydroxypropyl-β-cyclodextrin (per 200 mg tecovirimat/20 mL solution) is eliminated in the urine. It is known that clearance of hydroxypropyl-β-cyclodextrin is reduced in patients with mild, moderate, and severe renal impairment, resulting in higher exposure to hydroxypropyl-β-cyclodextrin; in these patients, half-life values are increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropyl-β-cyclodextrin until steady state is reached. In patients with mild (defined as creatinine clearance 60-89 mL/min) and moderate (defined as creatinine clearance 30-59 mL/min) renal impairment, Tpoxx® Injection should be used with caution. Creatinine clearance should be closely monitored and, if renal toxicity is suspected, consideration should be given to administering Tpoxx® orally if possible or to using an alternative medication. Tpoxx® Injection is contraindicated in patients with severe renal impairment.

Pediatric patients Tpoxx® Injection: In pediatric patients less than 2 years of age, there are limited data regarding the use of hydroxypropyl-β-cyclodextrin. Given that renal tubular function rapidly matures over the first few years of life, clearance of hydroxypropyl-β-cyclodextrin may be reduced in young pediatric patients, resulting in higher exposure to hydroxypropyl-β-cyclodextrin. Tpoxx® Injection should be used with caution in this population given that animal studies have shown potential for nephrotoxicity at very high exposure levels of hydroxypropyl-β-cyclodextrin. Given the potential for drug accumulation due to renal immaturity in pediatric patients less than 2 years, monitoring of renal function after treatment is recommended.

CONTRAINDICATIONS

Tpoxx® Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min).

Clinical Pharmacology

MECHANISMS OF ACTION

Tecovirimat is an antiviral drug against variola (smallpox) virus.

Dose & Administration

ADULTS

- 3 kg to less than 35 kg: 6 mg/kg every 12 hours by intravenous infusion over 6 hours for up to 14 days.
- 35 kg to less than 120 kg: 200 mg every 12 hours by intravenous infusion over 6 hours for up to 14 days.
- 120 kg and above: 300 mg every 12 hours by intravenous infusion over 6 hours for up to 14 days.

PEDIATRICS

Refer the adult dosing.

Pediatric patients weighing 13 kg or more should be switched to Tpoxx® Capsules to complete the 14-day treatment course as soon as oral therapy can be tolerated.

GERIATRICS

Refer the adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

A single-dose vial containing 200 mg of tecovirimat in 20 mL for further dilution prior to intravenous infusion.